

Oncology: Contents

Q: Diagnostic Tumor Markers and Their Role in Management of Specific Childhood Cancers	3
Q: Define tumour lysis syndrome. Enlist its important constituents. Outline its etiology and describe the management.....	6
Q: How will you prevent occurrence of tumour lysis syndrome	7
Q: Treatment of Tumor Lysis Syndrome.....	8
Q: Metabolic Emergencies in Pediatric Malignancies: Approach and Management.....	12
Q: Management of a Child with Acute Leukemia: Specific Treatment Regimens.....	14
Q: Treatment and Prognosis of Acute Lymphoblastic Leukemia (ALL)	16
Q: Management of CNS Leukemia	17
Q: Prognostic Indicators in Acute Leukemia	19
Q: ALL cytogenetics and risk stratification	21
Q: Utility of Immunophenotyping in the Diagnosis of Leukemia in Children	23
Q: Classification of Childhood Leukemias	24
Q: Management of Acute Myeloid Leukemia (AML) in Children	26
Q: Treatment of Chronic Myeloid Leukemia (CML) in Children.....	28
Q: Different Types of Lymphomas in Children and Their Histopathological Classification ..	30
Q: Clinical Features and Diagnosis of Posterior Cranial Fossa Tumors in Children	31
Q: Neuroblastoma: Diagnosis and Clinical Features	33
Q: Treatment of Neuroblastoma.....	36
Q: Paraneoplastic Syndromes in Children	40
Q: Opsoclonus Myoclonus Syndrome (OMS)	42
Q: Clinical Presentation and Management of Wilms Tumor	44
Q: Classification of Childhood Histiocytosis	46

Q: Describe the diagnostic criteria, clinical manifestations and treatment for hemophagocytic lymphohistiocytosis (HLH). What are the infections associated with it...	47
Q: Describe the clinical manifestations, diagnosis and treatment of Langerhan's cell histiocytosis.....	49
Q: Enumerate oncological emergencies in newly diagnosed leukemia.....	50
Q: Next-Generation Sequencing (NGS) in pediatric hemato-oncology	54
Q: Cytogenetics in acute leukemia.....	56
Q: Risk stratification of a newly diagnosed acute lymphatic leukemia.....	58
Q: Management of tumour lysis syndrome.	60
Q: JMML	61
Q: CLL (chronic lymphocytic leukemia).....	64



---X-----X---

Q: Diagnostic Tumor Markers and Their Role in Management of Specific Childhood Cancers

Tumor markers are integral in the diagnosis, staging, and management of various childhood cancers.

Alpha-fetoprotein (AFP)

- **Associated Cancers:** Hepatoblastoma, Yolk Sac Tumor
- **Role in Management:** Monitoring treatment response, detecting recurrence

Beta-human chorionic gonadotropin (β -hCG)

- **Associated Cancers:** Choriocarcinoma, Germ Cell Tumors
- **Role in Management:** Diagnosis, monitoring treatment efficacy, and detecting recurrence

Carcinoembryonic Antigen (CEA)

- **Associated Cancers:** Medullary Thyroid Cancer
- **Role in Management:** Post-operative monitoring for recurrence

Neuron-Specific Enolase (NSE)

- **Associated Cancers:** Neuroblastoma
- **Role in Management:** Monitoring treatment response and disease progression

Lactate Dehydrogenase (LDH)

- **Associated Cancers:** Lymphomas, Ewing Sarcoma
- **Role in Management:** Prognostic indicator, monitoring treatment response

CA-125

- **Associated Cancers:** Ovarian Tumors
- **Role in Management:** Monitoring for recurrence post-treatment

Thyroglobulin

- **Associated Cancers:** Differentiated Thyroid Cancer
- **Role in Management:** Post-thyroidectomy monitoring for recurrence

Calcitonin

- **Associated Cancers:** Medullary Thyroid Cancer
- **Role in Management:** Diagnostic and prognostic marker, monitoring for recurrence

Chromogranin A

- **Associated Cancers:** Neuroendocrine Tumors
- **Role in Management:** Diagnostic marker, monitoring treatment response

BCR-ABL Fusion Protein

- **Associated Cancers:** Chronic Myeloid Leukemia
- **Role in Management:** Confirming diagnosis, monitoring response to tyrosine kinase inhibitors

CD20

- **Associated Cancers:** Non-Hodgkin Lymphoma
- **Role in Management:** Target for monoclonal antibody therapy (Rituximab)

Philadelphia Chromosome

- **Associated Cancers:** Acute Lymphoblastic Leukemia (ALL)
- **Role in Management:** Guides treatment with tyrosine kinase inhibitors

Minimal Residual Disease (MRD) Testing

- **Associated Cancers:** ALL, AML
- **Role in Management:** Risk stratification, guiding intensity of chemotherapy

Isocitrate Dehydrogenase (IDH) Mutations

- **Associated Cancers:** Gliomas
- **Role in Management:** Target for specific inhibitors, prognostic indicator

BRAF V600E Mutation

- **Associated Cancers:** Melanoma, Langerhans Cell Histiocytosis
- **Role in Management:** Target for specific inhibitors like Vemurafenib

JAK2 Mutation

- **Associated Cancers:** Myeloproliferative Disorders

- **Role in Management:** Diagnostic and prognostic marker, target for JAK inhibitors

Biomarker	Associated Cancers	Role in Management
<i>Alpha-fetoprotein (AFP)</i>	Hepatoblastoma, Yolk Sac Tumor	Monitoring treatment response, detecting recurrence
<i>Beta-human chorionic gonadotropin (β-hCG)</i>	Choriocarcinoma, Germ Cell Tumors	Diagnosis, monitoring treatment efficacy, detecting recurrence
<i>Carcinoembryonic Antigen (CEA)</i>	Medullary Thyroid Cancer	Post-operative monitoring for recurrence
<i>Neuron-Specific Enolase (NSE)</i>	Neuroblastoma	Monitoring treatment response and disease progression
<i>Lactate Dehydrogenase (LDH)</i>	Lymphomas, Ewing Sarcoma	Prognostic indicator, monitoring treatment response
<i>CA-125</i>	Ovarian Tumors	Monitoring for recurrence post-treatment
<i>Thyroglobulin</i>	Differentiated Thyroid Cancer	Post-thyroidectomy monitoring for recurrence
<i>Calcitonin</i>	Medullary Thyroid Cancer	Diagnostic and prognostic marker, monitoring for recurrence
<i>Chromogranin A</i>	Neuroendocrine Tumors	Diagnostic marker, monitoring treatment response
<i>BCR-ABL Fusion Protein</i>	Chronic Myeloid Leukemia	Confirming diagnosis, monitoring response to tyrosine kinase inhibitors
<i>CD20</i>	Non-Hodgkin Lymphoma	Target for monoclonal antibody therapy (Rituximab)
<i>Philadelphia Chromosome</i>	Acute Lymphoblastic Leukemia (ALL)	Guides treatment with tyrosine kinase inhibitors
<i>Minimal Residual Disease (MRD) Testing</i>	ALL, AML	Risk stratification, guiding intensity of chemotherapy
<i>Isocitrate Dehydrogenase (IDH) Mutations</i>	Gliomas	Target for specific inhibitors, prognostic indicator
<i>BRAF V600E Mutation</i>	Melanoma, Langerhans Cell Histiocytosis	Target for specific inhibitors like Vemurafenib
<i>JAK2 Mutation</i>	Myeloproliferative Disorders	Diagnostic and prognostic marker, target for JAK inhibitors

---X-----X---

Q: Define tumour lysis syndrome. Enlist its important constituents. Outline its etiology and describe the management.

Tumor Lysis Syndrome: Definition

Tumor Lysis Syndrome (TLS) is a life-threatening oncological emergency characterized by the rapid release of intracellular components into the bloodstream following the lysis of malignant cells.

Important Constituents

- **Hyperkalemia:** Elevated potassium levels
- **Hyperphosphatemia:** Elevated phosphate levels
- **Hyperuricemia:** Elevated uric acid levels
- **Hypocalcemia:** Reduced calcium levels

Etiology

- **Chemotherapy:** Rapid cell death post-chemotherapy in hematologic malignancies like leukemia and lymphoma.
- **Radiation Therapy:** Especially in large tumor burdens.
- **Spontaneous TLS:** Rare, occurs without intervention, usually in high-grade malignancies.
- **Targeted Therapies:** Monoclonal antibodies and tyrosine kinase inhibitors can also induce TLS.

Management

Prophylactic Measures

- **Hydration:** Aggressive intravenous fluids to maintain urine output.
- **Allopurinol or Rasburicase:** To lower uric acid levels.
- **Electrolyte Monitoring:** Frequent monitoring of serum electrolytes.

Hyperkalemia Management

- **Calcium Gluconate:** For cardiac membrane stabilization.
- **Sodium Polystyrene Sulfonate:** To remove excess potassium.
- **Dialysis:** In severe cases.

Hyperphosphatemia Management

- **Phosphate Binders:** Such as calcium acetate.
- **Dialysis:** In severe cases.

Hyperuricemia Management

- **Allopurinol:** Inhibits xanthine oxidase, reducing uric acid production.
- **Rasburicase:** Enzyme that converts uric acid to a more soluble form.

Hypocalcemia Management

- **Calcium Supplementation:** Only in symptomatic cases due to risk of calcium-phosphate precipitation.

Monitoring and Supportive Care

- **Electrocardiogram (ECG):** To monitor for arrhythmias.
- **Intensive Care Unit (ICU) Admission:** For severe cases requiring close monitoring.

---X-----X---

Q: How will you prevent occurrence of tumour lysis syndrome

Prevention of TLS is crucial and involves a multi-pronged approach that starts even before the initiation of cancer therapy.

Prevention of Tumor Lysis Syndrome:

Risk Stratification

- **Identify High-Risk Patients:** Those with high tumor burden, sensitive tumors, and pre-existing renal dysfunction.

Pre-treatment Measures

- **Hydration:** Aggressive intravenous hydration to dilute released cellular contents and maintain renal function.
- **Alkalinization of Urine:** Using sodium bicarbonate to prevent uric acid and calcium phosphate crystals from forming in the renal tubules.

Pharmacological Interventions

- **Allopurinol:**
 - Inhibits xanthine oxidase, thereby reducing uric acid production.
 - Dose: 100-300 mg/m²/day orally, up to a maximum of 800 mg/day.
- **Rasburicase:**

- Catalyzes the conversion of uric acid to allantoin, a more soluble compound.
- Dose: 0.1-0.2 mg/kg as a single IV infusion over 30 minutes.

Electrolyte Management

- **Monitor Serum Levels:** Frequent monitoring of potassium, phosphate, calcium, and uric acid levels.
- **Correct Imbalances:** Use medications like calcium gluconate for hypocalcemia or sodium polystyrene sulfonate for hyperkalemia as needed.

Renal Function

- **Monitor Renal Function:** Through serum creatinine and urine output.
- **Avoid Nephrotoxic Agents:** Such as aminoglycosides and nonsteroidal anti-inflammatory drugs (NSAIDs).

Dialysis Consideration

- **Early Consultation with Nephrology:** For patients at high risk or those with pre-existing renal dysfunction.

Close Monitoring

- **Frequent Lab Tests:** To catch any imbalances early.
- **ECG Monitoring:** To detect cardiac arrhythmias due to electrolyte imbalances.

Patient Education: **Symptom Awareness:** Educate patients and caregivers about symptoms like muscle cramps, palpitations, or confusion, which could indicate electrolyte imbalances.

Multi-disciplinary Approach: **Involve Multiple Specialties:** Including oncology, nephrology, and critical care for comprehensive care.

---X-----X---

Q: Treatment of Tumor Lysis Syndrome

Initial Stabilization

- **Airway, Breathing, Circulation (ABCs):** Immediate stabilization of vital signs and functions.

Fluid Resuscitation

- **Aggressive Hydration:** IV fluids at 3,000 mL/ m²/day to maintain urine output at 100 mL/m²/hour.

Electrolyte Management

- **Hyperkalemia:**
 - Calcium gluconate for cardiac membrane stabilization.
 - Sodium polystyrene sulfonate to remove excess potassium.
 - Insulin and glucose to shift potassium intracellularly.
- **Hyperphosphatemia:**
 - Phosphate binders like calcium acetate.
 - Dialysis if severe.
- **Hypocalcemia:**
 - IV calcium gluconate or calcium chloride, but cautiously to avoid calcium-phosphate precipitation in kidneys.

Pharmacological Interventions

- **Allopurinol:**
 - Dose: 100-300 mg/ m²/day orally, up to a maximum of 800 mg/day.
 - Mechanism: Inhibits xanthine oxidase, reducing uric acid production.
- **Rasburicase:**
 - Dose: 0.1-0.2 mg/kg as a single IV infusion over 30 minutes.
 - Mechanism: Converts uric acid to allantoin, a more soluble compound.
- **Febuxostat:**
 - Alternative to allopurinol for patients with renal insufficiency.
 - Dose: 40-80 mg/day.

Renal Support

- **Continuous Renal Replacement Therapy (CRRT):** For severe cases with renal failure.
- **Hemodialysis:** For patients with severe hyperkalemia, hyperphosphatemia, or hypocalcemia unresponsive to medical treatment.

Monitoring

- **Frequent Lab Tests:** Serum electrolytes, renal function, uric acid, and lactate dehydrogenase (LDH) levels.
- **ECG Monitoring:** To detect cardiac arrhythmias due to electrolyte imbalances.

Adjunctive Therapies

- **Antiemetics:** To manage nausea and vomiting.
- **Antihypertensives:** To control high blood pressure, often using calcium channel blockers or beta-blockers.

Long-term Management

- **Follow-up Care:** Regular monitoring for chronic kidney disease, cardiac issues, and other long-term complications.

Multi-disciplinary Approach

- **Consultations:** Involve nephrology, oncology, and critical care teams for comprehensive management.

Patient and Family Education

- **Educate on Signs and Symptoms:** Such as muscle cramps, palpitations, or confusion, which could indicate complications.

Oncological Emergencies in Leukemia/Lymphomas

List of Emergencies

1. **Tumor Lysis Syndrome**
2. **Hyperleukocytosis and Leukostasis**
3. **Spinal Cord Compression**
4. **Superior Vena Cava Syndrome**
5. **Neutropenic Sepsis**
6. **Hemorrhagic Complications**
7. **Disseminated Intravascular Coagulation (DIC)**
8. **Hypercalcemia of Malignancy**
9. **Bone Marrow Failure**
10. **Metabolic Emergencies (e.g., hypoglycemia, lactic acidosis)**

By approaching each oncological emergency with a targeted yet comprehensive strategy, outcomes can be significantly improved.

Approach to Management

Tumor Lysis Syndrome

- **Hydration:** Aggressive IV fluids to maintain urine output.
- **Electrolyte Management:** Monitor and correct potassium, calcium, and phosphate levels.
- **Urate Lowering:** Allopurinol for prophylaxis; Rasburicase for acute management.
- **Dialysis:** Consider in severe cases with renal failure.

Hyperleukocytosis and Leukostasis

- **Leukapheresis:** To rapidly reduce WBC count.
- **Chemotherapy:** Initiate cytoreductive chemotherapy immediately.
- **Supportive Care:** Oxygen therapy, hydration, and alkalinization of urine.

Spinal Cord Compression

- **Corticosteroids:** Dexamethasone to reduce edema.
- **Imaging:** Urgent MRI to confirm diagnosis.
- **Surgical/Radiation:** Decompressive surgery followed by radiation or primary radiation therapy.

Superior Vena Cava Syndrome

- **Head Elevation:** To reduce venous pressure.
- **Corticosteroids:** To reduce inflammation and edema.
- **Radiation Therapy:** Urgent treatment to shrink the tumor.

Neutropenic Sepsis

- **Antibiotics:** Immediate broad-spectrum antibiotics.
- **Hemodynamic Support:** Fluid resuscitation, vasopressors if needed.
- **G-CSF:** Granulocyte-colony stimulating factor for neutrophil recovery.

Hemorrhagic Complications

- **Platelet Transfusion:** For severe thrombocytopenia.

- **Coagulation Factors:** Fresh frozen plasma for coagulopathy.
- **Hemostatic Agents:** Tranexamic acid in severe bleeding.

Disseminated Intravascular Coagulation (DIC)

- **Underlying Cause:** Treat leukemia/lymphoma aggressively.
- **Coagulation Support:** Fresh frozen plasma, platelets, and sometimes low-dose heparin.

Hypercalcemia of Malignancy

- **IV Hydration:** Saline infusion to dilute calcium.
- **Bisphosphonates:** Zoledronic acid or pamidronate.
- **Dialysis:** In severe, refractory cases.

Bone Marrow Failure

- **Transfusion:** Red cell and platelet transfusion.
- **Growth Factors:** Erythropoietin, G-CSF.
- **Antibiotics:** Prophylactic antibiotics to prevent infection.

Metabolic Emergencies

- **Correct Acid-Base Balance:** Bicarbonate infusion for acidosis.
- **Electrolyte Correction:** Potassium, calcium, and magnesium replacement.

General Principles

- **Multi-disciplinary Approach:** Oncology, critical care, hematology, and radiology teams should be involved.
- **Monitoring:** Continuous monitoring of vital signs, laboratory parameters, and response to treatment.
- **Patient Education:** Detailed explanation of the emergency, treatment options, and potential complications.

---X-----X---

Q: Metabolic Emergencies in Pediatric Malignancies: Approach and Management

Aim is to approach with timely identification, aggressive management, and continuous monitoring to optimize patient outcomes.

Hypercalcemia

- **Identification:** Serum calcium >11 mg/dL.

- **Initial Management:** IV hydration with isotonic saline, loop diuretics.
- **Pharmacotherapy:** Bisphosphonates like pamidronate or zoledronic acid.
- **Monitoring:** Frequent serum calcium, renal function tests, and ECG.

Tumor Lysis Syndrome

- **Risk Stratification:** Assess for high tumor burden and sensitivity to chemotherapy.
- **Prophylaxis:** Hydration, allopurinol or rasburicase.
- **Active Management:** Electrolyte correction, renal replacement therapy if needed.
- **Monitoring:** Serum uric acid, potassium, phosphate, and calcium levels.

Hyperammonemia

- **Identification:** Elevated blood ammonia levels, often with altered mental status.
- **Initial Management:** Hemodialysis or hemofiltration.
- **Pharmacotherapy:** Sodium benzoate, sodium phenylacetate.
- **Monitoring:** Serial ammonia levels, neurological status.

Hypoglycemia

- **Identification:** Blood glucose <60 mg/dL.
- **Initial Management:** IV dextrose bolus.
- **Maintenance:** Continuous glucose infusion.
- **Monitoring:** Frequent blood glucose checks, monitor for rebound hypoglycemia.

Lactic Acidosis

- **Identification:** Low pH, elevated lactate >5 mmol/L.
- **Initial Management:** IV fluids, correct hypoxia.
- **Pharmacotherapy:** Sodium bicarbonate for severe acidemia.
- **Monitoring:** Serial lactate and pH levels, hemodynamic monitoring.

Electrolyte Imbalances (Hyponatremia, Hyperkalemia)

- **Identification:** Serum sodium <135 mmol/L or potassium >5.5 mmol/L.

- **Initial Management:** Fluid restriction for hyponatremia, calcium gluconate for hyperkalemia.
- **Pharmacotherapy:** Hypertonic saline or sodium bicarbonate; sodium polystyrene sulfonate or hemodialysis for hyperkalemia.
- **Monitoring:** Serial electrolyte levels, ECG monitoring for hyperkalemia.

Respiratory Alkalosis

- **Identification:** Elevated pH, low pCO₂.
- **Initial Management:** Address underlying cause, usually hyperventilation.
- **Pharmacotherapy:** Sedation if anxiety-induced, mechanical ventilation adjustments.
- **Monitoring:** Serial arterial blood gases, respiratory rate.

General Principles

- **Multi-disciplinary Team:** Involve oncology, critical care, and metabolic specialists.
- **Early Identification:** Use of point-of-care testing and frequent lab monitoring.
- **Patient/Family Education:** Explain the nature of the emergency, treatment plan, and potential complications.

-----X-----X-----

Q: Management of a Child with Acute Leukemia: Specific Treatment Regimens Acute Lymphoblastic Leukemia (ALL)

- **Induction Phase:**
 - Vincristine: 1.5 mg/m² weekly for 4 weeks
 - Prednisone: 40 mg/m²/day for 28 days
 - Daunorubicin: 25 mg/m² weekly for 4 weeks
 - Asparaginase: 6000 IU/m² for 6 doses
- **Consolidation Phase:**
 - High-dose Methotrexate: 5g/m² over 24 hours
 - 6-Mercaptopurine: 60 mg/m²/day for 14 days

- **Maintenance Phase:**

- 6-Mercaptopurine: $50 \text{ mg/m}^2/\text{day}$
- Methotrexate: $20 \text{ mg/m}^2/\text{week}$
- Vincristine and Prednisone pulses every 4 weeks

Acute Myeloid Leukemia (AML)

- **Induction Phase:**

- Cytarabine: $100 \text{ mg/m}^2/\text{day}$ for 7 days
- Daunorubicin: $60 \text{ mg/m}^2/\text{day}$ for 3 days

- **Consolidation Phase:**

- High-dose Cytarabine: 3g/m^2 every 12 hours for 6 doses

- **Maintenance Phase:** Generally not used in AML

Supportive Care

- **G-CSF:** To expedite neutrophil recovery post-chemotherapy
- **Antibiotics:** Prophylactic antibiotics like ciprofloxacin
- **Antifungals:** Prophylactic antifungals like fluconazole

CNS Prophylaxis

- Intrathecal Methotrexate: 12 mg/m^2 at each lumbar puncture

Relapse Management

- **Salvage Chemotherapy:** FLAG-IDA regimen (Fludarabine, Cytarabine, G-CSF, and Idarubicin)
- **Allogeneic Stem Cell Transplant:** For eligible patients

Monitoring and Follow-Up

- **Minimal Residual Disease (MRD):** Flow cytometry or PCR
- **Cardiac Function:** Echocardiograms to monitor for anthracycline toxicity

Oncological Emergencies

- **Tumor Lysis Syndrome:** Allopurinol or Rasburicase, aggressive hydration
- **Hyperleukocytosis:** Leukapheresis and hydration

---X-----X---

Q: Treatment and Prognosis of Acute Lymphoblastic Leukemia (ALL)

Treatment Modalities

- **Induction Therapy**
 - Vincristine: 1.5 mg/m^2 weekly for 4 weeks
 - Prednisone: $40 \text{ mg/m}^2/\text{day}$ for 28 days
 - Daunorubicin: 25 mg/m^2 weekly for 4 weeks
 - Asparaginase: 6000 IU/m^2 for 6 doses
- **Consolidation Therapy**
 - High-dose Methotrexate: 5 g/m^2 over 24 hours
 - 6-Mercaptopurine: $60 \text{ mg/m}^2/\text{day}$ for 14 days
- **Maintenance Therapy**
 - 6-Mercaptopurine: $50 \text{ mg/m}^2/\text{day}$
 - Methotrexate: $20 \text{ mg/m}^2/\text{week}$
 - Vincristine and Prednisone pulses every 4 weeks
- **CNS Prophylaxis**
 - Intrathecal Methotrexate: 12 mg/m^2 at each lumbar puncture
- **Supportive Care**
 - G-CSF: To expedite neutrophil recovery
 - Antibiotics and Antifungals: Prophylactic measures
- **Relapse Management**
 - FLAG-IDA regimen (Fludarabine, Cytarabine, G-CSF, and Idarubicin)
 - Allogeneic Stem Cell Transplant

Risk Stratification

- **Standard Risk:** Age 1-9 years, WBC $<50,000/\mu\text{L}$
- **High Risk:** Age <1 or >9 years, WBC $>50,000/\mu\text{L}$
- **Very High Risk:** Induction failure, CNS or testicular involvement

Monitoring and Follow-Up

- **Minimal Residual Disease (MRD):** Flow cytometry or PCR
- **Cardiac Function:** Echocardiograms for anthracycline toxicity
- **Bone Marrow Aspirate:** To assess remission status

Prognostic Factors

- **Positive Prognostic Indicators**
 - Age between 1-9 years
 - Low WBC count at diagnosis
 - Rapid response to induction therapy
 - Negative MRD post-induction
- **Negative Prognostic Indicators**
 - Age <1 or >9 years
 - High WBC count at diagnosis
 - Presence of certain cytogenetic abnormalities (e.g., t(9;22))

Survival Rates

- **Standard Risk:** 5-year survival >90%
- **High Risk:** 5-year survival 75-90%
- **Very High Risk:** 5-year survival <75%

Future Directions

- **Immunotherapy:** CAR-T cell therapy for relapsed or refractory ALL

---X-----X---

Q: Management of CNS Leukemia

Diagnostic Evaluation

- **Lumbar Puncture:** Essential for confirming CNS involvement. It helps in the identification of leukemia cells in the cerebrospinal fluid (CSF).
- **MRI Brain:** Provides detailed imaging to assess for CNS lesions. Useful for planning radiation therapy if needed.
- **Flow Cytometry:** Utilized to characterize leukemia cells in CSF. Helps in guiding targeted therapy.

Risk Stratification

- **CNS1:** No blasts in CSF
- **CNS2:** <5 WBCs/ μ L and blasts present
- **CNS3:** Clinical signs of CNS leukemia or >5 WBCs/ μ L with blasts
- **CNS Isolated Relapse:** CNS relapse without bone marrow involvement

Treatment Modalities

- **Intrathecal Chemotherapy**
 - Methotrexate: 12-15 mg/m²
 - Cytarabine: 30-50 mg/m²
 - Hydrocortisone: 16-24 mg/m²
- **Systemic Chemotherapy**
 - High-dose Methotrexate: 5g/m² over 24 hours
 - High-dose Cytarabine: 2-3g/m² every 12 hours for 4 doses
- **Radiation Therapy**
 - Cranial Radiation: 18-24 Gy for CNS3 or isolated relapse
- **Stem Cell Transplant**
 - Indicated in refractory or relapsed cases

Supportive Care

- **Antibiotics:** Prophylaxis against bacterial meningitis
- **Antiepileptics:** For seizure management
- **Corticosteroids:** To reduce intracranial pressure

Monitoring and Follow-Up

- **Serial Lumbar Punctures:** To assess treatment response
- **MRI Scans:** To monitor for CNS lesions
- **Neurocognitive Assessments:** To evaluate long-term neurotoxicity

Prognostic Factors

- **Positive Prognostic Indicators**
 - Rapid clearance of blasts from CSF

- Absence of neurological symptoms
- **Negative Prognostic Indicators**
 - High initial WBC count in CSF
 - Presence of neurological deficits

Future Directions

- **Targeted Therapies:** FLT3 inhibitors, BTK inhibitors
- **Immunotherapy:** Intrathecal CAR-T cell therapy

---X-----X---

Q: Prognostic Indicators in Acute Leukemia

Age at Diagnosis

- Younger patients, especially those between 1-10 years, generally have a better prognosis.
- Infants and Older adults (>60 years) often have a poorer outcome due to comorbidities and less tolerance to aggressive therapies.

White Blood Cell Count at Diagnosis

- A high WBC count ($>100,000/\mu\text{L}$) is often associated with a poorer prognosis.
- Lower counts are generally favorable but must be interpreted in the context of other factors.

Cytogenetic and Molecular Abnormalities

- Philadelphia chromosome, t(9;22), is a poor prognostic factor in ALL.
- Favorable cytogenetics include t(8;21) and inv(16) in AML.
- FLT3, NPM1, and CEBPA mutations have specific prognostic implications.

Central Nervous System (CNS) Involvement

- CNS involvement at diagnosis is a poor prognostic indicator.
- Requires aggressive CNS-directed therapy.

Response to Initial Therapy

- Rapid early response to induction therapy is favorable.

- Minimal residual disease (MRD) assessment post-induction is critical for risk stratification.

Immunophenotype

- B-lineage ALL generally has a better prognosis than T-lineage.
- In AML, the presence of CD34, a stem cell marker, is associated with a poorer prognosis.

Serum Lactate Dehydrogenase (LDH) Levels

- Elevated LDH levels are generally associated with a higher tumor burden and poorer prognosis.

Extramedullary Disease

- Presence of leukemia cutis, chloromas, or other extramedullary involvement often indicates aggressive disease.

Performance Status

- Patients with a good performance status are more likely to tolerate aggressive therapies, which often leads to better outcomes.

Coagulopathy

- Presence of disseminated intravascular coagulation (DIC) is a poor prognostic factor, especially in AML.

Socioeconomic Factors

- Access to healthcare, compliance, and ability to tolerate treatment can also influence outcomes.

Multi-Drug Resistance (MDR) Gene Expression

- Overexpression of MDR genes can lead to chemotherapy resistance.

FAB Classification in AML

- M3 (APL) generally has the best prognosis, while M0, M5, M6, and M7 have a poorer prognosis.

Risk Stratification

- Many leukemia treatment protocols use a combination of these factors to stratify patients into different risk categories, which guides the aggressiveness of therapy.

---X-----X---

Q: ALL cytogenetics and risk stratification**Cytogenetics in ALL**

1. **Philadelphia Chromosome ($t(9;22)(q34;q11.2)$):**
 - The most well-known cytogenetic abnormality in ALL.
 - Results in the BCR-ABL1 fusion gene.
 - Associated with a poor prognosis in adults but less so in children.
 - Targeted therapy with tyrosine kinase inhibitors (TKIs) like imatinib has significantly improved outcomes.
2. **Hyperdiploidy:**
 - Presence of more than 50 chromosomes in leukemia cells.
 - Generally associated with a favorable prognosis, especially in children.
 - High hyperdiploidy (51-65 chromosomes) is particularly favorable.
3. **Hypodiploidy:**
 - Fewer than 44 chromosomes.
 - Associated with a poor prognosis.
 - Near-haploidy (23-29 chromosomes) and low hypodiploidy (30-39 chromosomes) are particularly high-risk.
4. **$t(12;21)(p13;q22)$ ETV6-RUNX1 Fusion:**
 - Most common in children and associated with a good prognosis.
 - Often presents with a low white blood cell count at diagnosis.
5. **$t(1;19)(q23;p13.3)$ TCF3-PBX1 Fusion:**
 - Found in both children and adults.
 - Historically considered high-risk, but outcomes have improved with modern chemotherapy regimens.
6. **MLL (Mixed Lineage Leukemia) Gene Rearrangements:**
 - Common in infants and associated with a poor prognosis.
 - Includes various translocations involving the MLL gene on chromosome 11q23.
7. **Intrachromosomal Amplification of Chromosome 21 (iAMP21):**

- Identified as a distinct entity with a poor prognosis.
- Requires intensified therapy.

8. **Other Abnormalities:**

- Deletions of 6q, 9p, and 13q, and abnormalities of 8q24 (MYC gene) can be seen.
- Their prognostic significance is less clear and often considered in the context of other features.

Risk Stratification in ALL

1. **Risk Groups:**

- **Standard Risk:** Generally includes patients with hyperdiploidy, ETV6-RUNX1 fusion, and no adverse features.
- **High Risk:** Includes patients with features like hypodiploidy, MLL rearrangements, BCR-ABL1 fusion, iAMP21, and certain clinical features (e.g., high white blood cell count, age <1 year or >10 years, poor response to initial therapy).

2. **Treatment Implications:**

- Risk stratification guides treatment intensity.
- High-risk patients often require more intensive chemotherapy and may be candidates for hematopoietic stem cell transplantation.
- The use of targeted therapies like TKIs for BCR-ABL1 positive ALL.

3. **Minimal Residual Disease (MRD):**

- MRD assessment is increasingly used for risk stratification.
- Detects residual leukemia cells during or after treatment.
- High levels of MRD are associated with a higher risk of relapse.

4. **Age and WBC Count at Diagnosis:**

- Older age and higher WBC count at diagnosis are traditionally associated with a worse prognosis.

5. **Response to Therapy:**

- Early response to therapy, measured by MRD, is a critical prognostic factor.

---X-----X---

Q: Utility of Immunophenotyping in the Diagnosis of Leukemia in Children

Immunophenotyping is more than just another test; it's a tool that provides a comprehensive understanding of the leukemia's characteristics. This information is invaluable for clinicians as they navigate the complexities of diagnosis, treatment planning, and ongoing management in pediatric leukemia.

Identification of Cell Lineage

- Distinguishes between lymphoid and myeloid leukemia.
- Helps in sub-classifying ALL into B-ALL or T-ALL.

Risk Stratification

- Certain immunophenotypes are associated with good or poor prognostic outcomes.
- Enables personalized treatment plans.

Minimal Residual Disease (MRD) Detection

- Highly sensitive in detecting MRD post-treatment.
- Guides adjustments in treatment intensity.

Differential Diagnosis

- Helps in distinguishing leukemia from other hematologic disorders.
- Useful in cases where morphology and cytochemistry are inconclusive.

Monitoring Treatment Response

- Changes in immunophenotype can indicate clonal evolution or emergence of resistant clones.
- Enables timely intervention.

Therapeutic Target Identification

- Identifies potential targets for immunotherapies like monoclonal antibodies.

Relapse Prediction

- Early changes in immunophenotype can predict impending relapse.
- Allows for preemptive treatment modifications.

Facilitates Stem Cell Transplant Decisions

- Provides information that can guide the selection of donors and conditioning regimens.

Aids in Research and Clinical Trials

- Provides a standardized method for categorizing leukemia subtypes.
- Facilitates the development of new targeted therapies.

---X-----X---

Q: Classification of Childhood Leukemias

Based on Cell Lineage

1. *Lymphoblastic Leukemias*

- Acute Lymphoblastic Leukemia (ALL)
 - B-cell ALL
 - T-cell ALL

2. *Myeloid Leukemias*

- Acute Myeloid Leukemia (AML)
- Chronic Myeloid Leukemia (CML)

Based on Molecular and Cytogenetic Features

1. *ALL*

- Hyperdiploid (>50 chromosomes)
- Hypodiploid (<44 chromosomes)
- t(9;22) Philadelphia chromosome
- t(12;21) ETV6-RUNX1
- t(1;19) TCF3-PBX1

2. *AML*

- t(8;21) AML1-ETO
- Inv(16) CBF β -MYH11
- t(15;17) PML-RARA
- FLT3-ITD mutations

Based on Risk Stratification

1. **Standard Risk**

- Favorable cytogenetics
- Good response to initial therapy

2. **High Risk**

- Unfavorable cytogenetics
- Poor response to initial therapy

Based on Age at Diagnosis

1. **Infant Leukemia**

- Diagnosed before age 1
- Often associated with MLL gene rearrangements

2. **Childhood Leukemia**

- Diagnosed between ages 1-18
- Most commonly ALL

3. **Adolescent and Young Adult (AYA) Leukemia**

- Diagnosed between ages 15-39
- Higher incidence of AML and poor-risk ALL

Based on Clinical Presentation

1. **Localized**

- Limited to bone marrow and peripheral blood

2. **Systemic**

- Involvement of liver, spleen, and lymph nodes

3. **CNS Involvement**

- Leukemic cells in cerebrospinal fluid

4. **Testicular Involvement**

- Rare, but specific to males and requires targeted therapy

-----X-----X-----

Q: Management of Acute Myeloid Leukemia (AML) in Children

Induction Therapy

1. Chemotherapy Regimens

- Cytarabine (Ara-C)
- Daunorubicin or Idarubicin
- Etoposide
- Mitoxantrone

2. Targeted Therapy

- FLT3 inhibitors like Midostaurin for FLT3-ITD mutations

3. Supportive Care

- Antibiotics for infection control
- Blood and platelet transfusions

Consolidation Therapy

1. High-Dose Cytarabine

- Backbone of consolidation

2. Allogeneic Stem Cell Transplant

- For high-risk or relapsed cases

3. Additional Chemotherapy

- Anthracyclines, Etoposide, or Fludarabine

Maintenance Therapy

1. Low-Dose Chemotherapy

- Cytarabine, 6-Mercaptopurine

2. Targeted Agents

- Sorafenib for FLT3-ITD mutations

Relapsed or Refractory AML

1. Salvage Chemotherapy

- FLAG-IDA (Fludarabine, Cytarabine, G-CSF, Idarubicin)

2. Second Allogeneic Transplant

- For relapsed post-transplant cases

3. **Clinical Trials**

- Investigational agents like Gemtuzumab Ozogamicin

Supportive Measures

1. **Antibiotic Prophylaxis**

- To prevent bacterial infections

2. **Antifungal Agents**

- Prophylaxis against fungal infections

3. **Growth Factors**

- G-CSF to stimulate neutrophil recovery

4. **Nutritional Support**

- Parenteral or enteral nutrition

5. **Psychosocial Support**

- Counseling and emotional support

Monitoring and Follow-up

1. **Bone Marrow Aspirate**

- To assess remission status

2. **Minimal Residual Disease (MRD)**

- Flow cytometry or PCR

3. **Regular Blood Counts**

- To monitor recovery and detect relapse

4. **Imaging Studies**

- For extramedullary disease

5. **Late Effects Monitoring**

- Cardiac, endocrine, and neurocognitive assessments

Prognostic Factors

1. **Cytogenetics**

- t(8;21), Inv(16) are favorable

2. **Molecular Markers**

- NPM1, CEBPA are favorable; FLT3-ITD is unfavorable

3. **Response to Therapy**

- Early response is a positive indicator

4. **MRD Status**

- Negative MRD post-induction is favorable

-----X-----X-----

Q: Treatment of Chronic Myeloid Leukemia (CML) in Children

Initial Evaluation and Risk Stratification

1. **Complete Blood Count**

- Baseline evaluation

2. **Bone Marrow Aspiration and Biopsy**

- Confirm diagnosis

3. **Cytogenetic and Molecular Analysis**

- Identify BCR-ABL1 translocation

4. **Risk Stratification**

- Sokal, Hasford, or EUTOS score

Pharmacological Management

1. **Tyrosine Kinase Inhibitors (TKIs)**

- Imatinib Mesylate: First-line treatment
- Dasatinib: Second-line or for T315I mutation
- Nilotinib: Second-line
- Bosutinib: Third-line

2. **Dose Adjustments**

- Based on response and tolerability

3. **Combination Therapy**

- TKIs with Hydroxyurea or Interferon-alpha

Monitoring and Response Assessment

1. **Hematologic Response**

- Complete blood count every 2-4 weeks

2. **Cytogenetic Response**

- Bone marrow evaluation at 3, 6, and 12 months

3. **Molecular Response**

- qPCR for BCR-ABL1 transcript levels

Allogeneic Stem Cell Transplant (SCT)

1. **Indications**

- Failure to achieve remission with TKIs
- Progression to blast crisis

2. **Donor Selection**

- HLA-matched sibling or unrelated donor

3. **Conditioning Regimen**

- Myeloablative or reduced-intensity

Supportive Care

1. **Management of Side Effects**

- Nausea, fluid retention, myelosuppression

2. **Infection Prophylaxis**

- Antibiotics and antifungals

3. **Nutritional Support**

- Dietary consultation

Long-Term Follow-up

1. **Regular Monitoring**

- Blood counts, liver and renal function tests

2. **Assessment for Late Effects**

- Cardiovascular, endocrine, and growth

3. **Psychosocial Support**

- Counseling and educational support

Resistance and Relapse

1. *Mutation Analysis*

- Identify resistant mutations

2. *Switch to Second or Third-Generation TKIs*

- Dasatinib, Nilotinib, or Bosutinib

3. *Clinical Trials*

- Investigational agents or combinations

-----X-----X-----

Q: Different Types of Lymphomas in Children and Their Histopathological Classification

The classification is based on the cell of origin, morphological features, and specific molecular markers.

Hodgkin Lymphoma (HL)

1. *Classical Hodgkin Lymphoma*

- Nodular Sclerosis: Most common in adolescents, characterized by lacunar cells
- Mixed Cellularity: Common in younger children, Reed-Sternberg cells present
- Lymphocyte-rich: Rare, best prognosis, Reed-Sternberg cells with lymphocytic background
- Lymphocyte-depleted: Least common, worst prognosis, aggressive

2. *Nodular Lymphocyte-Predominant Hodgkin Lymphoma (NLPHL)*

- Popcorn cells: Variant of Reed-Sternberg cells
- Favorable prognosis

Non-Hodgkin Lymphoma (NHL)

1. *B-Cell NHL*

- Burkitt Lymphoma: "Starry sky" appearance, MYC translocation
- Diffuse Large B-Cell Lymphoma: Large, transformed B cells; CD20 positive

- Primary Mediastinal B-Cell Lymphoma: Thymic origin, often localized

2. *T-Cell NHL*

- Anaplastic Large Cell Lymphoma: Hallmark cells, ALK-positive/negative variants
- Lymphoblastic Lymphoma: TdT positive, often confused with T-ALL
- Peripheral T-Cell Lymphoma: Heterogeneous group, poor prognosis

3. *Rare Types*

- Mantle Cell Lymphoma: Cyclin D1 overexpression
- Follicular Lymphoma: BCL2 translocation, indolent course

Other Lymphomas

1. *Primary CNS Lymphoma*

- Usually diffuse large B-cell type, confined to CNS

2. *Cutaneous Lymphomas*

- Mycosis fungoides: T-cell origin, skin lesions
- Primary cutaneous B-cell lymphoma: B-cell origin, localized to skin

Composite Lymphomas: Coexistence of HL and NHL in the same tissue

---X---

X---

Q: Clinical Features and Diagnosis of Posterior Cranial Fossa Tumors in Children

Clinical Features

1. *Headache*

- Morning headaches, worsens with position change
- Often associated with nausea and vomiting

2. *Ataxia*

- Unsteady gait, clumsiness
- Difficulty with fine motor skills

3. *Nystagmus*

- Involuntary eye movements
- Horizontal, vertical, or rotary

4. *Cranial Nerve Dysfunction*

- Facial weakness, hearing loss
- Dysphagia, hoarseness

5. *Papilledema*

- Swelling of the optic disc
- Due to increased intracranial pressure

6. *Cognitive and Behavioral Changes*

- Irritability, personality changes
- Decline in school performance

7. *Hydrocephalus*

- Accumulation of cerebrospinal fluid
- Leads to increased head size in infants

8. *Focal Neurological Deficits*

- Hemiparesis, sensory loss
- Depending on the tumor location

9. *Seizures*

- Less common, focal or generalized

Diagnostic Modalities

1. *MRI Brain*

- Gold standard
- T1, T2, FLAIR sequences for detailed anatomy

2. *CT Scan*

- Useful when MRI is contraindicated
- May reveal calcifications

3. *Lumbar Puncture*

- Contraindicated in increased intracranial pressure
- For cytological analysis

4. *Cerebral Angiography*

- To assess blood supply to the tumor
- Rarely used nowadays

5. **EEG**

- If seizures are a presenting symptom
- To rule out other causes

6. **Audiometry**

- For tumors affecting auditory pathway
- Baseline and follow-up

7. **Biopsy**

- Histopathological confirmation
- Stereotactic or open

8. **Tumor Markers**

- Alpha-fetoprotein, beta-HCG
- Useful in germ cell tumors

9. **Genetic and Molecular Testing**

- For targeted therapy
- Increasingly important in modern oncology

10. **Bone Scan and PET-CT**

- For metastatic evaluation
- Especially in high-grade tumors

---X-----X---

Q: Neuroblastoma: Diagnosis and Clinical Features

Clinical Features

1. **Abdominal Mass**

- Palpable, non-tender
- Most common in adrenal gland origin

2. **Systemic Symptoms**

- Fever, weight loss, malaise
- Often mistaken for infection

3. **Bone Pain**

- Limb pain, refusal to walk
- Due to metastasis to bones

4. **Hepatomegaly**

- Enlarged liver
- Secondary to liver involvement or paraneoplastic syndrome

5. **Respiratory Distress**

- Due to mediastinal mass
- May cause stridor or wheezing

6. **Horner's Syndrome**

- Ptosis, miosis, anhidrosis
- Tumor involvement of sympathetic chain

7. **Opsoclonus-Myoclonus Syndrome**

- Rapid, involuntary eye movements
- Associated with ataxia and myoclonus

8. **Skin Lesions**

- Blueberry muffin spots
- Cutaneous metastasis

9. **Hypertension**

- Secondary to catecholamine secretion
- May be paroxysmal

10. **Anemia and Thrombocytosis**

- Due to bone marrow involvement
- May present with fatigue and easy bruising

Diagnostic Modalities

1. **Ultrasound**

- Initial imaging for abdominal mass
- Can differentiate solid vs cystic nature

2. **CT/MRI**

- Detailed anatomical imaging
- Useful for surgical planning

3. **Metaiodobenzylguanidine (MIBG) Scan**

- Specific for neuroblastoma
- Helps in staging and follow-up

4. **Biopsy**

- Histopathological confirmation
- May include immunohistochemistry

5. **Bone Marrow Aspiration/Biopsy**

- To assess marrow involvement
- Important for staging

6. **Urine Catecholamines**

- VMA, HVA levels
- Useful for diagnosis and monitoring

7. **Serum LDH and Ferritin**

- Elevated in advanced disease
- Prognostic indicators

8. **FISH Analysis**

- For MYCN amplification
- Important prognostic factor

9. **PET-CT**

- For metastatic evaluation
- Especially in high-risk cases

10. **Genetic Testing**

- ALK mutations -For targeted therapies

Q: Treatment of Neuroblastoma.

The treatment of neuroblastoma, a complex pediatric malignancy arising from neural crest cells, involves a multimodal approach.

- The treatment of neuroblastoma requires a highly specialized and individualized approach, involving a multidisciplinary team of pediatric oncologists, surgeons, radiologists, pathologists, and supportive care specialists.
- Advances in molecular biology and immunotherapy have significantly improved outcomes, especially in high-risk neuroblastoma.
- The strategy is tailored based on the stage of the disease, age of the patient, MYCN oncogene status, and other biological features.

Treatment Modalities:

1. **Surgery:**

- Primary modality for localized tumors.
- Goals: Complete resection of the tumor, when feasible.
- In advanced cases: Debulking surgery to reduce tumor burden.

2. **Chemotherapy:**

- Induction Chemotherapy: For high-risk cases to shrink the tumor before surgery.
- Common Agents: Cyclophosphamide, doxorubicin, vincristine, etoposide, and carboplatin.
- Maintenance Chemotherapy: In cases of residual disease post-surgery.

3. **Radiation Therapy:**

- Indications: Incomplete resection, metastatic disease, or relapsed neuroblastoma.
- Techniques: External beam radiation therapy (EBRT), MIBG (metaiodobenzylguanidine) therapy for tumors that take up MIBG.

4. **High-Dose Chemotherapy with Stem Cell Transplant:**

- Used in high-risk neuroblastoma.
- Autologous Stem Cell Transplant: Following high-dose chemotherapy to restore bone marrow.

5. **Immunotherapy:**

- Anti-GD2 Antibodies: Dinutuximab combined with GM-CSF and IL-2.
- Mechanism: Targeting GD2, a disialoganglioside expressed on neuroblastoma cells.

6. **Retinoid Therapy:**

- 13-cis-Retinoic Acid (Isotretinoin): Used in maintenance therapy.
- Mechanism: Induces differentiation of neuroblastoma cells.

7. **Targeted Therapy:**

- ALK Inhibitors: For patients with ALK mutations.
- Other Molecularly Targeted Agents: Based on specific genetic aberrations in the tumor.

Treatment Based on Risk Stratification:

- **Low-Risk Neuroblastoma:**
 - Surgery alone in many cases.
 - Observation or minimal chemotherapy in some cases.
- **Intermediate-Risk Neuroblastoma:**
 - Surgery and moderate chemotherapy.
 - Radiation therapy in selected cases.
- **High-Risk Neuroblastoma:**
 - Intensive multimodal therapy:
 - Induction chemotherapy.
 - Surgery.
 - High-dose chemotherapy with stem cell rescue.
 - Radiation therapy.
 - Immunotherapy with anti-GD2 antibody.
 - Retinoid therapy for maintenance.

Supportive Care:

- **Management of Side Effects:**

- Nausea, vomiting, and alopecia from chemotherapy.
- Infection prevention and management.
- Nutritional support.
- **Pain Management:**
 - Analgesics and supportive measures for tumor-related pain.
- **Psychosocial Support:**
 - Counseling and support for the patient and family.

Follow-up and Monitoring:

- **Regular Follow-up:**
 - Monitoring for recurrence and late effects of treatment.
 - Imaging and laboratory tests as per protocol.
- **Long-term Monitoring:**
 - For late effects of treatment like growth and developmental delays, hearing loss, and secondary malignancies.

Q: Treatment of Neuroblastoma (5 marks)

Risk Stratification

- **Low Risk:** Surgery alone or observation
- **Intermediate Risk:** Surgery + Chemotherapy
- **High Risk:** Intensive multimodal therapy

Surgical Management

1. **Primary Tumor Resection**
 - Complete or partial resection
 - Depends on tumor location and extent
2. **Lymph Node Dissection**
 - For staging and prognosis

Chemotherapy

1. **Low-Risk**

- May not require chemotherapy

2. **Intermediate-Risk**

- Regimens: COJEC, OPEC, or OJEC
- Agents: Carboplatin, Etoposide, Cyclophosphamide

3. **High-Risk**

- Induction: CAV/IE alternating with CE
- Agents: Cisplatin, Doxorubicin, Etoposide, Ifosfamide

Radiation Therapy

1. **Local Control**

- For residual disease post-surgery
- Dose: 21-36 Gy

2. **Metastatic Sites**

- For bone or CNS involvement

Immunotherapy

1. **Anti-GD2 Antibody (*Dinutuximab*)**

- For high-risk patients
- Combined with GM-CSF or IL-2

2. **Checkpoint Inhibitors**

- Experimental, for relapsed or refractory cases

Stem Cell Transplant

1. **Autologous Stem Cell Transplant**

- For high-risk cases
- Post-induction chemotherapy

2. **Allogeneic Stem Cell Transplant**

- Experimental, for relapsed or refractory cases

Targeted Therapies

1. **ALK Inhibitors (*Crizotinib*)**

- For ALK-positive tumors

2. **Retinoic Acid**

- For differentiation therapy in high-risk cases

Supportive Care

1. **G-CSF or GM-CSF**

- For neutropenia

2. **Blood and Platelet Transfusions**

- For anemia and thrombocytopenia

3. **Pain Management**

- Opioids, NSAIDs

4. **Nutritional Support**

- Enteral or parenteral nutrition

Follow-Up and Monitoring

1. **Regular Imaging**

- MRI, CT, MIBG scans

2. **Biochemical Monitoring**

- Urinary catecholamines, serum LDH

3. **Bone Marrow Aspirate**

- For residual disease assessment

-----X-----X-----

Q: Paraneoplastic Syndromes in Children

- ✚ Paraneoplastic syndromes in children are rare but serious complications often indicating an underlying malignancy.
- ✚ They can affect various systems including neurological, endocrine, hematologic, and cutaneous.
- ✚ Diagnosis requires a high index of suspicion and is confirmed by identifying the underlying malignancy.
- ✚ Treatment is primarily aimed at treating the underlying cancer, but symptomatic treatment is also crucial.

Etiology

- **Neuroblastoma**: Most common in children
- **Leukemia and Lymphoma**: Second most common
- **Wilms' Tumor**: Rare but documented
- **Rhabdomyosarcoma**: Extremely rare

Neurological Paraneoplastic Syndromes

1. **Opsoclonus-Myoclonus Syndrome**: Associated with neuroblastoma
2. **Limbic Encephalitis**: Rare, associated with Hodgkin's lymphoma
3. **Cerebellar Ataxia**: Seen in Hodgkin's and non-Hodgkin's lymphoma
4. **Acute Disseminated Encephalomyelitis (ADEM)**: Rare, seen in leukemia

Endocrine Paraneoplastic Syndromes

1. **SIADH (Syndrome of Inappropriate Antidiuretic Hormone)**: Common in small cell lung cancer, rare in pediatric malignancies
2. **Hypercalcemia**: Seen in neuroblastoma and rhabdomyosarcoma
3. **Cushing Syndrome**: ACTH secretion, rare in children

Hematologic Paraneoplastic Syndromes

1. **Anemia**: Common in many cancers
2. **Thrombocytosis**: Seen in neuroblastoma
3. **Disseminated Intravascular Coagulation (DIC)**: Seen in acute promyelocytic leukemia

Cutaneous Paraneoplastic Syndromes

1. **Dermatomyositis**: Rare, associated with lymphoma
2. **Erythema Nodosum**: Seen in Hodgkin's lymphoma

Diagnostic Workup

1. **Tumor Markers**: AFP, beta-HCG
2. **Imaging**: MRI, CT, Ultrasound
3. **Biopsy**: To confirm malignancy
4. **CSF Analysis**: For neurological syndromes
5. **Endocrine Tests**: Serum electrolytes, cortisol levels

Treatment

Targeting the Underlying Cancer

1. **Surgery:** Resection of the tumor
2. **Chemotherapy:** Depending on the type of cancer
3. **Radiation:** For localized tumors

Symptomatic Management

1. **Corticosteroids:** For neurological and cutaneous symptoms
2. **IVIg:** For immune-mediated syndromes
3. **Desmopressin:** For SIADH

Prognosis

- **Variable:** Depends on the underlying malignancy and the effectiveness of its treatment
- **Poor Prognosis:** Usually indicates advanced or aggressive cancer

-----X-----X-----

Q: Opsoclonus Myoclonus Syndrome (OMS)

Opsoclonus Myoclonus Syndrome is a rare, often paraneoplastic, neurological disorder characterized by opsoclonus, myoclonus, and ataxia. Diagnosis is clinical but requires a thorough workup to identify underlying causes, especially neuroblastoma in children.

Etiology

- **Paraneoplastic Syndrome:** Often associated with **neuroblastoma**
- **Autoimmune:** Anti-Ri, Anti-Hu antibodies
- **Viral Infections:** Epstein-Barr, Coxsackie
- **Idiopathic:** In some cases, the cause remains unknown

Clinical Presentation

1. **Opsoclonus:** Rapid, involuntary eye movements
2. **Myoclonus:** Sudden, brief muscle jerks
3. **Ataxia:** Lack of muscle coordination
4. **Behavioral Changes:** Irritability, sleep disturbances

5. **Speech Disturbances:** Slurred speech, mutism

Diagnostic Workup

1. **MRI Brain:** To rule out CNS lesions
2. **CSF Analysis:** Elevated protein, pleocytosis
3. **Autoantibody Testing:** Anti-Ri, Anti-Hu
4. **Tumor Screening:** Abdominal ultrasound, CT, MRI for neuroblastoma
5. **EEG:** To rule out seizure disorders

Treatment

Immune Therapies

1. **Corticosteroids:** Prednisone, Methylprednisolone
2. **IVIG:** Intravenous immunoglobulin
3. **Plasmapheresis:** For refractory cases

Immunomodulatory Agents

1. **Rituximab:** Anti-CD20 monoclonal antibody
2. **Cyclophosphamide:** Immunosuppressive agent

Symptomatic Treatment

1. **Clonazepam:** For myoclonus control
2. **Antihistamines:** For sleep disturbances

Tumor Treatment

1. **Surgery:** If neuroblastoma is present
2. **Chemotherapy:** If associated with malignancy

Supportive Care

1. **Physical Therapy:** For ataxia and motor skills
2. **Speech Therapy:** For speech disturbances

Prognosis

- **Variable:** Depends on underlying cause
- **Long-term Neurological Sequelae:** Common, especially if treatment is delayed

Follow-Up

1. **Regular Neurological Assessments:** To monitor symptoms
2. **Imaging:** To monitor for tumor recurrence if applicable
3. **Autoantibody Levels:** To assess treatment response

---X-----X---

Q: Clinical Presentation and Management of Wilms Tumor

- ✚ Wilms tumor is the most common renal malignancy in children, often presenting with an abdominal mass and sometimes with hematuria, hypertension, and other symptoms.
- ✚ Diagnosis is primarily radiological, and treatment involves a combination of surgery, chemotherapy, and sometimes radiation.
- ✚ The prognosis is generally good for early-stage disease but decreases with higher stages and metastasis.

Clinical Presentation

1. **Abdominal Mass:** Most common sign, usually palpable and non-tender
2. **Hematuria:** Microscopic or gross, occurs in about 25% of cases
3. **Abdominal Pain:** Less common, may indicate tumor rupture
4. **Hypertension:** Due to renin secretion by the tumor
5. **Fever:** Present in some cases, mechanism unclear
6. **Anemia:** Due to chronic disease or hemorrhage
7. **Weight Loss and Malaise:** Less common, indicative of advanced disease
8. **Varicocele:** Rare, may indicate left renal vein thrombosis
9. **Polycythemia:** Extremely rare, secondary to erythropoietin production

Diagnostic Workup

1. **Ultrasound:** Initial imaging modality
2. **CT/MRI:** For staging and surgical planning
3. **Biopsy:** Not usually done preoperatively due to risk of tumor spillage
4. **Urinalysis:** To check for hematuria
5. **CBC:** To assess for anemia
6. **Chest X-ray:** To rule out metastasis
7. **Serum Chemistry:** For baseline renal function

Staging

1. **Stage I:** Tumor confined to kidney and completely resected
2. **Stage II:** Tumor extends beyond kidney but completely resected
3. **Stage III:** Residual non-hematogenous tumor present postoperatively
4. **Stage IV:** Hematogenous metastases
5. **Stage V:** Bilateral renal involvement

Treatment

Surgical Management

1. **Nephrectomy:** Standard treatment for localized disease
2. **Lymph Node Sampling:** For staging

Chemotherapy

1. **Actinomycin-D and Vincristine:** For Stage I and II
2. **Doxorubicin:** Added for Stage III and IV
3. **Ifosfamide and Carboplatin:** For relapsed or refractory cases

Radiation Therapy

1. **Flank Radiation:** For Stage III
2. **Whole Lung Irradiation:** For pulmonary metastasis

Targeted Therapy

1. **Sunitinib:** For advanced or recurrent cases
2. **Irinotecan and Temozolomide:** For relapsed disease

Prophylactic Measures

1. **Regular Follow-up:** To monitor for recurrence
2. **Renal Function Tests:** Long-term monitoring

Prognosis

1. **Excellent for Stage I and II:** 90% survival rate
2. **Variable for Stage III and IV:** 50-70% survival rate
3. **Poor for Stage V:** Requires bilateral nephrectomy and transplant

---X-----X---

Q: Classification of Childhood Histiocytosis

Childhood histiocytosis a wide range of disorders characterized by the proliferation of histiocytes. Classified into Langerhans Cell Histiocytosis (LCH) and Non-Langerhans Cell Histiocytosis, each with its own subtypes based on the systems involved and the risk profile.

Malignant forms like Histiocytic Sarcoma and Langerhans Cell Sarcoma are rare but aggressive.

Langerhans Cell Histiocytosis (LCH)

1. Single-System LCH

- Unifocal: Involves a single site (e.g., bone, skin)
- Multifocal: Multiple sites within one system (e.g., multiple bones)

2. Multi-System LCH

- Low-risk: Involves skin, bones, lymph nodes, and hypothalamus
- High-risk: Involves liver, spleen, and bone marrow

Non-Langerhans Cell Histiocytosis

1. Hemophagocytic Lymphohistiocytosis (HLH)

- Primary (Familial)
- Secondary (Associated with infections, malignancies)

2. Juvenile Xanthogranuloma (JXG)

- Cutaneous
- Systemic

3. Rosai-Dorfman Disease (RDD)

- Cutaneous
- Extranodal
- Nodal

4. Erdheim-Chester Disease (ECD)

- Skeletal
- Extra-skeletal

5. *Sea-Blue Histiocyte Syndrome*

- Primary
- Secondary (Associated with lipid metabolism disorders)

6. *Benign Cephalic Histiocytosis*

- Cutaneous
- Systemic (Rare)

Malignant Histiocytosis

1. *Histiocytic Sarcoma*

- Localized
- Disseminated

2. *Langerhans Cell Sarcoma*

- Localized
- Disseminated

Miscellaneous

1. *Indeterminate Cell Histiocytosis*

- Cutaneous; Systemic

2. *Reticuloendotheliosis*

- Cutaneous; Systemic

-----X-----X-----

Q: Describe the diagnostic criteria, clinical manifestations and treatment for hemophagocytic lymphohistiocytosis (HLH). What are the infections associated with it.

HLH is a severe, life-threatening condition that requires prompt diagnosis and aggressive treatment. The diagnostic criteria are comprehensive, involving clinical, laboratory, and histological parameters. Treatment is multifaceted, involving chemotherapy, immunosuppression, and supportive care. Various infections can trigger or be associated with HLH, making antimicrobial therapy a crucial component of management.

Diagnostic criteria:

1. **Fever:** Persistent high fever ($>38.5^{\circ}\text{C}$)
2. **Splenomegaly:** Clinically or radiologically detected
3. **Cytopenias:** Affecting at least two of three lineages (hemoglobin <9 g/dL, platelets $<100,000/\mu\text{L}$, neutrophils $<1,000/\mu\text{L}$)
4. **Hypertriglyceridemia and/or Hypofibrinogenemia:** Triglycerides ≥ 265 mg/dL, fibrinogen ≤ 150 mg/dL
5. **Hemophagocytosis:** In bone marrow, spleen, or lymph nodes without evidence of malignancy
6. **Low/absent NK-cell activity:** As measured by standard assays
7. **Ferritin:** Elevated levels (>500 ng/mL)
8. **Soluble CD25:** Elevated levels ($>2,400$ U/mL)

Note: At least five of the eight criteria must be fulfilled for diagnosis.

Clinical Manifestations

1. **Fever:** Persistent and high
2. **Hepatosplenomegaly:** Enlarged liver and spleen, usually spleno-hepatomegaly occurs
3. **Jaundice:** Due to liver involvement
4. **Rash:** Skin eruptions
5. **Neurological Symptoms:** Irritability, seizures, ataxia
6. **Respiratory Distress:** Due to lung involvement or ARDS
7. **Coagulopathy:** Bleeding, easy bruising
8. **Multi-organ Failure:** In severe cases

Treatment

1. **Chemotherapy Regimen:** Etoposide and dexamethasone are commonly used.
2. **Immunosuppression:** Cyclosporine A, anti-thymocyte globulin
3. **Intravenous Immunoglobulin (IVIG)**
4. **Antibiotics/Antivirals:** For associated infections
5. **Supportive Care:** Blood transfusions, electrolyte management
6. **Hematopoietic Stem Cell Transplant (HSCT):** For refractory or relapsed cases

Associated Infections

1. **Viral:** Epstein-Barr virus (EBV), Cytomegalovirus (CMV), Herpes simplex virus (HSV)
2. **Bacterial:** Staphylococcus, Streptococcus
3. **Fungal:** Candida, Aspergillus
4. **Parasitic:** Leishmania, Malaria

-----X-----X-----

Q: Describe the clinical manifestations, diagnosis and treatment of Langerhan's cell histiocytosis.

- ✚ The Langerhans Cell Histiocytosis is a rare and complex disorder with a wide range of clinical manifestations, from isolated skin or bone lesions to systemic involvement affecting multiple organs.
- ✚ Diagnosis is primarily histological, supported by immunohistochemical and radiographic studies.
- ✚ Treatment is individualised to the severity and extent of the disease, ranging from corticosteroids and chemotherapy to more aggressive interventions like radiotherapy and stem cell transplant.

Clinical Manifestations of Langerhans Cell Histiocytosis (LCH)

1. **Cutaneous Lesions:** Rash, eczema-like eruptions, or seborrheic dermatitis-like lesions
2. **Bone Lesions:** Pain, swelling, and lytic lesions on radiographs
3. **Hepatosplenomegaly:** Enlarged liver and spleen
4. **Lymphadenopathy:** Enlarged lymph nodes
5. **Pulmonary Symptoms:** Cough, dyspnea, and cystic lung changes on imaging
6. **Endocrine Abnormalities:** Diabetes insipidus due to pituitary involvement
7. **Neurological Symptoms:** Ataxia, irritability, seizures
8. **Otitis Media:** Chronic or recurrent, due to mastoid involvement
9. **Oral Manifestations:** Gingivitis, ulcers, and loose teeth

Diagnosis

1. **Histopathology:** Biopsy showing characteristic Langerhans cells with Birbeck granules

2. **Immunohistochemistry:** Positive for CD1a and S-100
3. **Radiographic Studies:** X-rays, CT scans, or MRIs for bone and lung lesions
4. **Endocrine Evaluation:** For diabetes insipidus, water deprivation test and ADH levels
5. **Complete Blood Count:** To assess for cytopenias
6. **Liver Function Tests:** Elevated in liver involvement
7. **Pulmonary Function Tests:** For lung involvement
8. **Bone Marrow Aspiration:** In cases with suspected systemic involvement

Treatment

1. **Corticosteroids:** Prednisone or prednisolone for initial control
2. **Chemotherapy:** Vincristine, etoposide, or cytarabine for severe or refractory cases
3. **Radiotherapy:** For isolated bone lesions or CNS involvement
4. **Surgical Resection:** For isolated lesions that are accessible
5. **Immunomodulators:** Thalidomide or interferon-alpha for skin lesions
6. **Hormone Replacement:** For endocrine abnormalities like diabetes insipidus
7. **Antibiotics:** For secondary infections
8. **Supportive Care:** Blood transfusions, hydration, and electrolyte management
9. **Hematopoietic Stem Cell Transplant:** For severe, refractory cases

-----X-----X-----

Q: Enumerate oncological emergencies in newly diagnosed leukemia

- ❖ Oncological emergencies in newly diagnosed leukemia are critical conditions that require immediate medical attention
- ❖ These emergencies arise due to the rapid proliferation of leukemic cells or as a consequence of treatment
- ❖ These emergencies represent a spectrum of potentially life-threatening complications that require immediate and coordinated care to optimize outcomes and reduce mortality in patients with newly diagnosed leukemia.

Hyperleukocytosis and Leukostasis

- **Definition:** Extremely high white blood cell count leading to blood viscosity and impaired microcirculation.

- **Clinical Manifestations:** Respiratory distress, altered mental status, visual changes, priapism.
- **Management:** Hydration, leukapheresis, cytoreductive therapy.

Tumor Lysis Syndrome (TLS)

- **Definition:** Metabolic abnormalities resulting from rapid lysis of malignant cells.
- **Clinical Manifestations:** Hyperuricemia, hyperkalemia, hyperphosphatemia, hypocalcemia, renal failure.
- **Management:** Aggressive hydration, allopurinol or rasburicase, electrolyte monitoring and correction.

Hemorrhagic Diathesis

- **Definition:** Coagulopathy and bleeding due to thrombocytopenia, disseminated intravascular coagulation (DIC), or direct infiltration of organs by leukemic cells.
- **Clinical Manifestations:** Petechiae, ecchymoses, mucosal bleeding, internal hemorrhage.
- **Management:** Platelet transfusions, fresh frozen plasma, control of DIC.

Neutropenic Fever and Infections

- **Definition:** Fever in a neutropenic patient, often indicating an underlying infection.
- **Clinical Manifestations:** Fever, signs of sepsis, may have site-specific symptoms (e.g., pneumonia, cellulitis).
- **Management:** Broad-spectrum antibiotics, antifungals, granulocyte colony-stimulating factor (G-CSF).

Anemia

- **Definition:** Reduced hemoglobin levels due to marrow infiltration or treatment-related myelosuppression.
- **Clinical Manifestations:** Fatigue, pallor, dyspnea, tachycardia.
- **Management:** Red blood cell transfusions, treatment of underlying cause.

Superior Vena Cava Syndrome (SVCS)

- **Definition:** Obstruction of the superior vena cava by leukemic mass.

- **Clinical Manifestations:** Facial and upper extremity swelling, dyspnea, cyanosis, distended neck veins.
- **Management:** Radiation therapy, chemotherapy, steroids, stenting.

Spinal Cord Compression

- **Definition:** Compression of the spinal cord due to leukemic infiltration.
- **Clinical Manifestations:** Back pain, motor weakness, sensory loss, bladder and bowel dysfunction.
- **Management:** Radiation therapy, high-dose steroids, neurosurgical evaluation.

Acute Renal Failure

- **Definition:** Renal impairment due to tumor lysis syndrome, nephrotoxic drugs, or leukemic infiltration.
- **Clinical Manifestations:** Oliguria, anuria, elevated creatinine and urea.
- **Management:** Hydration, avoidance of nephrotoxic agents, dialysis if needed.

Cardiac Tamponade

- **Definition:** Accumulation of fluid in the pericardial sac leading to impaired cardiac filling.
- **Clinical Manifestations:** Chest pain, dyspnea, hypotension, muffled heart sounds, elevated jugular venous pressure.
- **Management:** Pericardiocentesis, management of underlying leukemia.

Airway Obstruction

- **Definition:** Obstruction of the airways due to mediastinal mass or lymphadenopathy.
- **Clinical Manifestations:** Stridor, dyspnea, cough, respiratory distress.
- **Management:** Airway management, steroids, chemotherapy, radiation.
- **Prompt Recognition and Management:** Essential for improving outcomes.
- **Multidisciplinary Approach:** Involves hematologists, oncologists, intensivists, and other specialists.
- **Preventive Measures:** Such as prophylactic allopurinol in high-risk patients for TLS, can be crucial.

Emergency Type	Definition & Key Features	Clinical Manifestations	Management Strategies
<i>Hyperleukocytosis & Leukostasis</i>	Extremely high WBC count causing blood viscosity and impaired microcirculation.	Respiratory distress, altered mental status, visual changes, priapism.	Hydration, leukapheresis, cytoreductive therapy.
<i>Tumor Lysis Syndrome (TLS)</i>	Metabolic abnormalities from rapid lysis of malignant cells.	Hyperuricemia, hyperkalemia, hyperphosphatemia, hypocalcemia, renal failure.	Aggressive hydration, allopurinol/rasburicase, electrolyte monitoring and correction.
<i>Hemorrhagic Diathesis</i>	Coagulopathy and bleeding due to thrombocytopenia, DIC, or organ infiltration.	Petechiae, ecchymoses, mucosal bleeding, internal hemorrhage.	Platelet transfusions, fresh frozen plasma, control of DIC.
<i>Neutropenic Fever & Infections</i>	Fever in neutropenic patients, often indicating infection.	Fever, signs of sepsis, site-specific symptoms (e.g., pneumonia, cellulitis).	Broad-spectrum antibiotics, antifungals, G-CSF.
<i>Anemia</i>	Reduced hemoglobin levels due to marrow infiltration or treatment-related myelosuppression.	Fatigue, pallor, dyspnea, tachycardia.	Red blood cell transfusions, treatment of underlying cause.
<i>Superior Vena Cava Syndrome (SVCS)</i>	Obstruction of the superior vena cava by leukemic mass.	Facial/upper extremity swelling, dyspnea, cyanosis, distended neck veins.	Radiation therapy, chemotherapy, steroids, stenting.
<i>Spinal Cord Compression</i>	Compression of the spinal cord due to leukemic infiltration.	Back pain, motor weakness, sensory loss, bladder/bowel dysfunction.	Radiation therapy, high-dose steroids, neurosurgical evaluation.
<i>Acute Renal Failure</i>	Renal impairment due to TLS, nephrotoxic drugs, or leukemic infiltration.	Oliguria, anuria, elevated creatinine and urea.	Hydration, avoidance of nephrotoxic agents, dialysis if needed.
<i>Cardiac Tamponade</i>	Fluid accumulation in the pericardial sac impairing cardiac filling.	Chest pain, dyspnea, hypotension, muffled heart sounds, elevated JVP.	Pericardiocentesis, management of underlying leukemia.
<i>Airway Obstruction</i>	Obstruction of airways due to mediastinal mass or lymphadenopathy.	Stridor, dyspnea, cough, respiratory distress.	Airway management, steroids, chemotherapy, radiation.

---X-----X---

Q: Next-Generation Sequencing (NGS) in pediatric hemato-oncology

- ✚ Next-Generation Sequencing (NGS) in pediatric hemato-oncology is a rapidly evolving technology that has significantly impacted the diagnosis, risk stratification, and treatment of various hematologic and oncologic disorders in children
- ✚ NGS in pediatric hemato-oncology offers a comprehensive approach to understanding the genetic landscape of childhood cancers, enabling personalized medicine
- ✚ Its role is expanding with ongoing research and technological advancements, promising further improvements in patient outcomes.

1. *Diagnosis and Subtyping:*

- **Leukemias and Lymphomas:** NGS aids in identifying specific genetic mutations, translocations, or rearrangements, refining diagnosis and subtyping (e.g., BCR-ABL1 in ALL, MYC rearrangements in lymphomas).
- **Solid Tumors:** Identifies genetic alterations in tumors like neuroblastoma, brain tumors, and sarcomas, aiding in precise diagnosis and classification.

2. *Risk Stratification:*

- **Prognostic Implications:** Certain genetic mutations have prognostic significance (e.g., TP53 mutations, FLT3-ITD in AML) and guide risk stratification.
- **Minimal Residual Disease (MRD) Detection:** NGS can detect low levels of disease post-treatment, aiding in risk stratification and treatment decisions.

3. *Treatment Planning:*

- **Targeted Therapy:** Identifies actionable mutations that can be targeted by specific therapies (e.g., tyrosine kinase inhibitors in BCR-ABL1 positive ALL).
- **Immunotherapy:** NGS can identify neoantigens for potential immunotherapy targets.

4. *Monitoring and Relapse Detection:*

- **Early Detection of Relapse:** NGS can detect emerging clones or resistant mutations earlier than conventional methods.
- **Clonal Evolution:** Helps in understanding the evolution of malignancy and resistance mechanisms.

5. **Research and Clinical Trials:**

- **Biomarker Discovery:** NGS is instrumental in discovering new biomarkers for disease.
- **Clinical Trials:** Identifies patients eligible for specific targeted therapy trials based on genetic profiles.

6. **Genetic Predisposition Syndromes:**

- **Hereditary Cancer Syndromes:** NGS can identify germline mutations in genes associated with increased cancer risk (e.g., TP53 in Li-Fraumeni syndrome).
- **Bone Marrow Failure Syndromes:** Useful in diagnosing inherited marrow failure syndromes (e.g., mutations in DKC1 in dyskeratosis congenita).

7. **Hematopoietic Stem Cell Transplantation:**

- **Donor Matching:** NGS offers high-resolution HLA typing for donor selection.
- **Post-Transplant Monitoring:** Detects chimerism and emerging malignant clones post-transplant.

8. **Pharmacogenomics:**

- **Drug Metabolism and Toxicity:** Identifies genetic variants affecting drug metabolism and risk of toxicity (e.g., TPMT, NUDT15 variants affecting thiopurine metabolism).

9. **Ethical and Counseling Considerations:**

- **Informed Consent:** Essential due to the potential discovery of incidental findings.
- **Genetic Counseling:** Necessary for interpreting results, especially in the context of germline mutations.

-----X-----X-----

Q: Cytogenetics in acute leukemia

- ❖ Cytogenetics plays a crucial role in the diagnosis, risk stratification, and management of acute leukemia
- ❖ Cytogenetic analysis in acute leukemia is not only diagnostic but also prognostic and predictive, playing a pivotal role in personalized medicine
- ❖ It guides clinicians in tailoring treatment regimens, monitoring treatment response, and predicting outcomes
- ❖ As research advances, more genetic abnormalities are being identified, offering potential new targets for therapy and further refining risk stratification and management strategies.

Role of cytogenetics in acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML):

Acute Lymphoblastic Leukemia (ALL)

- **Philadelphia Chromosome ($t(9;22)(q34;q11)$):**
 - Found in B-cell ALL.
 - Associated with poor prognosis.
 - Treatment: Tyrosine kinase inhibitors (e.g., imatinib).
- **E2A-PBX1 ($t(1;19)(q23;p13)$):**
 - Common in pediatric ALL.
 - Generally associated with a good response to therapy.
- **TEL-AML1 ($t(12;21)(p13;q22)$):**
 - Most common in children; good prognosis.
 - Often responds well to standard chemotherapy.
- **MLL Rearrangements ($11q23$):**
 - Found in both ALL and AML.
 - Associated with poor prognosis in infants.
- **Hyperdiploidy (>50 chromosomes):**
 - Common in children; favorable prognosis.
 - Often sensitive to chemotherapy.
- **Hypodiploidy (<44 chromosomes):**
 - Associated with poor prognosis.

Acute Myeloid Leukemia (AML)

- ***t(8;21)(q22;q22), RUNX1-RUNX1T1:***
 - Associated with AML M2 subtype.
 - Generally favorable prognosis.
 - Sensitive to high-dose cytarabine.
- ***t(15;17)(q22;q12), PML-RARA:***
 - Defining feature of Acute Promyelocytic Leukemia (APL, AML M3).
 - Treatment: All-trans retinoic acid (ATRA) and arsenic trioxide.
- ***Inv(16)(p13.1q22) or t(16;16)(p13.1;q22), CBFB-MYH11:***
 - Associated with AML M4Eo subtype.
 - Favorable prognosis.
 - Responds well to high-dose cytarabine.
- ***FLT3 Mutations:***
 - Common in AML.
 - Associated with poor prognosis.
 - Treatment: FLT3 inhibitors.
- ***Complex Karyotype (≥3 chromosomal abnormalities):***
 - Generally associated with a poor prognosis.
- ***Monosomal Karyotype:***
 - Very poor prognosis.

General Considerations

- ***Risk Stratification:*** Cytogenetic analysis is essential for risk stratification in acute leukemia, guiding treatment decisions.
- ***Monitoring:*** Used to monitor disease progression and response to therapy.
- ***Prognostic Significance:*** Certain cytogenetic abnormalities are strongly associated with prognosis.
- ***Targeted Therapy:*** Some abnormalities guide the use of targeted therapies (e.g., tyrosine kinase inhibitors in Philadelphia chromosome-positive ALL).

- **Research and Emerging Therapies:** Ongoing research is identifying new cytogenetic markers and targeted therapies.

---X-----X---

Q: Risk stratification of a newly diagnosed acute lymphatic leukemia.

- ❖ Risk stratification in newly diagnosed acute lymphoblastic leukemia (ALL) is a critical process that guides treatment decisions and prognostication
- ❖ It involves assessing various factors to categorize patients into different risk groups, which can be broadly classified as standard risk, intermediate risk, and high risk
- ❖ Risk stratification in ALL is a dynamic process, evolving with ongoing research and clinical trials
- ❖ It's essential for tailoring treatment intensity: lower-risk patients may require less intensive therapy to reduce treatment-related morbidity, while higher-risk patients may need more aggressive treatment, including consideration for hematopoietic stem cell transplantation
- ❖ The ultimate goal is to maximize cure rates while minimizing short and long-term treatment-related complications.

1. Age at Diagnosis:

- **Standard Risk:** Typically, age 1-9 years.
- **High Risk:** Less than 1 year or older than 10 years.

2. White Blood Cell (WBC) Count at Diagnosis:

- **Standard Risk:** WBC count less than 50,000/ μ L.
- **High Risk:** WBC count greater than 50,000/ μ L.

3. Immunophenotyping:

- **B-cell ALL:** Generally has a better prognosis than T-cell ALL.
- **T-cell ALL:** Often considered higher risk.

4. Genetic Abnormalities:

- **Favorable Prognosis:** Hyperdiploidy, ETV6-RUNX1 fusion.
- **Poor Prognosis:** BCR-ABL1 fusion (Philadelphia chromosome), MLL rearrangements, hypodiploidy.

5. Response to Initial Therapy:

- **Standard Risk:** Rapid early response, minimal residual disease (MRD) negative.

- **High Risk:** Slow response, MRD positive after induction therapy.

6. Central Nervous System (CNS) Involvement:

- **Standard Risk:** No CNS involvement.
- **High Risk:** CNS involvement at diagnosis.

7. Testicular Involvement (in males):

- **High Risk:** Presence of testicular involvement at diagnosis.

8. Ethnicity and Race:

- Certain ethnic and racial groups may have different risk profiles, although this is a less definitive factor compared to others.

9. Other Clinical Features:

- **High Risk:** Features like a large mediastinal mass in T-cell ALL.

Risk Factor	Standard Risk	High Risk	Notes
Age at Diagnosis	1-9 years	<1 year or >10 years	Age is a significant prognostic factor in ALL.
WBC Count at Diagnosis	<50,000/ μ L	>50,000/ μ L	High WBC count is associated with poorer prognosis.
Immunophenotype	B-cell ALL	T-cell ALL	B-cell ALL generally has a better prognosis.
Genetic Abnormalities	Hyperdiploidy, ETV6-RUNX1 fusion	BCR-ABL1 fusion, MLL rearrangements, Hypodiploidy	Genetic markers play a crucial role in determining prognosis and treatment approach.
Response to Therapy	Rapid response, MRD negative	Slow response, MRD positive	Minimal residual disease (MRD) status post-induction is a key prognostic indicator.
CNS Involvement	No involvement	Presence at diagnosis	CNS involvement at diagnosis indicates a higher risk.

Testicular Involvement	Not applicable	Presence at diagnosis (in males)	Testicular involvement is a marker of high risk in male patients.
Ethnicity and Race	Variable	Variable	Certain ethnic and racial groups may have different risk profiles.
Other Clinical Features	Absence of high-risk features	Large mediastinal mass in T-cell ALL, etc.	Additional clinical features can influence risk stratification.

---X-----X---

Q: Management of tumour lysis syndrome.

- ❖ Tumor Lysis Syndrome (TLS) is a potentially life-threatening oncological emergency that occurs when tumor cells release their contents into the bloodstream, typically in response to cancer treatment
- ❖ Effective management of TLS involves both preventive measures and active treatment strategies
- ❖ Management of TLS requires a multidisciplinary approach, with prompt recognition and treatment of metabolic abnormalities
- ❖ Prophylactic measures are crucial in high-risk patients, and continuous monitoring is essential for early detection and management of complications
- ❖ The goal is to prevent renal failure and severe electrolyte imbalances, thereby reducing morbidity and mortality associated with TLS.

Preventive Measures:

- **Risk Assessment:** Identify high-risk patients (e.g., those with high tumor burden or sensitive to treatment like lymphomas, acute leukemias).
- **Hydration:** Aggressive intravenous hydration to maintain urine output and reduce the concentration of serum electrolytes. In high risk cases it is even started 48 hours prior to the initiation of cancer chemotherapy.
- **Allopurinol or Rasburicase:** Prophylactic administration to prevent hyperuricemia. Rasburicase is preferred in high-risk patients.
- **Monitoring:** Frequent monitoring of renal function, electrolytes (potassium, calcium, phosphate), and uric acid levels.

Active Treatment Strategies:

1. **Hyperkalemia:**

- **Mild to Moderate:** Sodium polystyrene sulfonate (Kayexalate), diuretics, oral/rectal bicarbonate.
- **Severe:** Insulin with glucose, calcium gluconate (for cardiac protection), beta-agonists, dialysis in refractory cases.

2. **Hyperphosphatemia and Hypocalcemia:**

- **Phosphate Binders:** Sevelamer, calcium acetate.
- **Avoid Calcium Supplements:** Unless symptomatic hypocalcemia.
- **Dialysis:** Considered if severe and refractory to medical management.

3. **Hyperuricemia:**

- **Rasburicase:** Especially in high-risk patients or those with established hyperuricemia.
- **Allopurinol:** In lower-risk patients or as prophylaxis.

4. **Acute Kidney Injury:**

- **Maintain Urine Output:** Diuretics if necessary.
- **Avoid Nephrotoxins:** NSAIDs, certain antibiotics.
- **Dialysis:** If indicated based on renal function and fluid overload.

5. **Monitoring and Supportive Care:**

- **Regular Monitoring:** Electrolytes, renal function, uric acid, and fluid balance.
- **Supportive Care:** Management of nausea, vomiting, and other symptoms.

6. **Dialysis:**

- **Indications:** Refractory hyperkalemia, hyperphosphatemia, significant renal impairment, or severe fluid overload.

-----X-----X-----

Q: JMML

- ✚ Juvenile Myelomonocytic Leukemia (JMML) is a rare and aggressive hematopoietic malignancy of early childhood, characterized by the overproduction of myelomonocytic cells.
- ✚ It falls under the category of myelodysplastic/myeloproliferative diseases and represents a unique clinical and biological entity with distinct pathophysiological mechanisms.
- ✚ JMML represents a challenging pediatric oncology entity due to its aggressive nature, complex pathophysiology, and limited treatment options.
- ✚ The management of JMML requires a multidisciplinary approach, encompassing accurate diagnosis, risk stratification, and an individualized treatment plan.
- ✚ Advances in our understanding of the molecular genetics of JMML are paving the way for novel therapeutic strategies, which are critically needed to improve outcomes for affected children.

Pathophysiology and Molecular Genetics

- **Clonal Hematopoietic Disorder:** JMML is a clonal disorder of hematopoietic progenitor cells. It exhibits both myelodysplastic and myeloproliferative features.
- **Genetic Abnormalities:** The disease is associated with various genetic abnormalities, including mutations in the RAS pathway (e.g., NF1, KRAS, NRAS), PTPN11, and CBL genes. These mutations lead to constitutive activation of the RAS-MAPK signaling pathway, driving uncontrolled cell proliferation.
- **Epigenetic Dysregulation:** Recent studies suggest a role for epigenetic dysregulation in JMML pathogenesis, although this area requires further exploration.

Clinical Presentation

- **Age of Onset:** Typically affects children under the age of four.
- **Symptoms:** Include fever, pallor, skin rash, hepatosplenomegaly, lymphadenopathy, and a propensity to develop infections.

- **Hematological Findings:** Characterized by leukocytosis with monocytosis, anemia, and thrombocytopenia. Bone marrow examination typically reveals hypercellularity with increased myelomonocytic cells.

Diagnostic Criteria

- **WHO Guidelines:** Diagnosis is based on clinical features, peripheral blood and bone marrow findings, and genetic studies.
- **Exclusion of Other Disorders:** Important to differentiate JMML from other childhood leukemias and myeloproliferative disorders.

Treatment and Prognosis

- **Chemotherapy:** Conventional chemotherapy has limited efficacy and is primarily used to stabilize the disease or as a bridge to more definitive treatment.
- **Hematopoietic Stem Cell Transplantation (HSCT):** Currently, the only curative treatment for JMML. However, the relapse rate post-transplantation remains significant.
- **Targeted Therapies:** Emerging research on targeted therapies, particularly inhibitors of the RAS pathway, offers potential new treatment avenues.
- **Prognostic Factors:** Factors such as age at diagnosis, platelet count, and specific genetic mutations can influence prognosis.

Drug/Therapy	Mechanism of Action	Role in JMML Treatment
Cytarabine (Ara-C)	Antimetabolite that interferes with DNA synthesis	Used in chemotherapy regimens, often as a bridge to hematopoietic stem cell transplantation (HSCT)
6-Mercaptopurine (6-MP)	Purine analog that inhibits DNA and RNA synthesis	May be used in combination with other chemotherapeutic agents for disease stabilization
Azacitidine	DNA methyltransferase inhibitor, induces hypomethylation of DNA	Investigated for its potential to modify disease course by targeting epigenetic dysregulation

Hydroxyurea	Inhibits ribonucleotide reductase, reducing DNA synthesis	Used for cytoreduction and control of leukocytosis
Interferon-alpha	Immunomodulatory agent	Has shown some efficacy in controlling symptoms and reducing spleen size
Ruxolitinib	JAK1/2 inhibitor	Being explored for its role in targeting aberrant JAK-STAT signaling in JMML
Sorafenib	Kinase inhibitor targeting RAF/MEK/ERK pathway	Investigational use in cases with specific mutations in the RAS pathway
Hematopoietic Stem Cell Transplantation (HSCT)	Replacement of the diseased marrow with healthy donor stem cells	Currently the only curative treatment option for JMML

- **Supportive Care:** In addition to these therapies, supportive care (e.g., management of infections, transfusions) is a critical component of JMML treatment.

Research and Future Directions

- **Molecularly Targeted Therapy:** Ongoing research is focused on developing targeted therapies that inhibit the aberrant signaling pathways in JMML.
- **Genomic Studies:** Comprehensive genomic studies are crucial for understanding the disease's heterogeneity and for the development of personalized medicine approaches.
- **Improving HSCT Outcomes:** Research is ongoing to improve the outcomes of HSCT, including reducing the risk of relapse and managing graft-versus-host disease.

---X-----X---

Q: CLL (chronic lymphocytic leukemia).

- ✚ Chronic Lymphocytic Leukemia (CLL) is a type of cancer that typically occurs in older adults, characterized by the accumulation of functionally incompetent lymphocytes

- ✦ It is extremely rare in children, and when it does occur, it presents unique diagnostic and therapeutic challenges
- ✦ CLL in children is a rare and poorly understood entity
- ✦ Its management in the pediatric population is challenging due to the lack of specific guidelines and is often guided by the principles of adult treatment
- ✦ A multidisciplinary approach involving pediatric oncologists, hematologists, geneticists, and supportive care teams is essential for the optimal management of pediatric CLL
- ✦ Continued research and clinical trials are vital for advancing our understanding and treatment of this rare pediatric malignancy.

Epidemiology and Etiology

- **Rare in Children:** CLL is predominantly a disease of the elderly, with most cases diagnosed in individuals over 50 years of age. Its occurrence in children is exceedingly rare.
- **Etiological Factors:** While the exact cause of CLL in children is unknown, genetic predispositions and environmental factors are considered potential contributors.

Pathophysiology

- **Clonal Proliferation:** CLL involves the clonal proliferation of B lymphocytes. These cells are typically functionally incompetent and have a longer lifespan, leading to their accumulation.
- **Genetic Abnormalities:** Chromosomal abnormalities such as deletions in 13q14, trisomy 12, and mutations in TP53 and IGHV genes are common in adult CLL but their prevalence in pediatric CLL is not well established.

Clinical Presentation

- **Asymptomatic Early Stage:** Many cases are asymptomatic and detected incidentally during routine blood tests.
- **Symptoms:** When present, symptoms may include lymphadenopathy, hepatosplenomegaly, fatigue, and increased susceptibility to infections.
- **Differential Diagnosis:** It's crucial to differentiate pediatric CLL from other more common pediatric leukemias like Acute Lymphoblastic Leukemia (ALL).

Diagnostic Evaluation

- **Peripheral Blood Smear:** Characteristic appearance of small, mature lymphocytes with a narrow border of cytoplasm.

- **Immunophenotyping:** Flow cytometry of peripheral blood reveals clonal B-cell populations with specific surface markers (CD19+, CD5+, CD23+).
- **Molecular and Cytogenetic Studies:** To identify genetic abnormalities and prognostic markers.

Treatment

- **Watchful Waiting:** In asymptomatic cases, immediate treatment may not be necessary.
- **Chemotherapy:** For symptomatic or progressive disease. Treatment regimens in children are extrapolated from adult data due to the rarity of the disease.
- **Targeted Therapies:** Agents like ibrutinib, a Bruton's tyrosine kinase inhibitor, are used in adults but their efficacy and safety in children are not well established.
- **Supportive Care:** Management of infections and other complications.

Treatment Type	Description	Indications/Notes
Watchful Waiting	Monitoring without active treatment until symptoms develop or disease progresses.	Used in early-stage CLL or asymptomatic patients.
Chemotherapy	Traditional chemotherapy agents like chlorambucil, fludarabine, cyclophosphamide.	Previously a standard treatment, now often combined with other therapies or used in specific patient groups.
Monoclonal Antibodies	Rituximab, ofatumumab, obinutuzumab target CD20 on B-cells.	Often combined with chemotherapy. Enhances immune-mediated killing of CLL cells.
Bruton's Tyrosine Kinase (BTK) Inhibitors	Ibrutinib, acalabrutinib block BTK, crucial for B-cell receptor signaling.	Used in frontline and relapsed/refractory settings. Effective in high-risk CLL.
BCL-2 Inhibitors	Venetoclax inhibits the BCL-2 protein, promoting apoptosis in CLL cells.	Effective in both frontline and relapsed/refractory CLL. Often used in combination with monoclonal antibodies.

<i>PI3K Inhibitors</i>	Idelalisib, duvelisib inhibit the PI3K pathway, important for survival of CLL cells.	Mainly used in relapsed/refractory CLL. Associated with specific side effects requiring monitoring.
<i>Allogeneic Stem Cell Transplant</i>	Replacement of the patient's bone marrow with donor stem cells.	Considered in young, fit patients with high-risk or refractory CLL. High risk of complications.
<i>Chimeric Antigen Receptor (CAR) T-Cell Therapy</i>	Genetically modified T-cells to target and kill CLL cells.	Emerging treatment for patients with relapsed/refractory CLL. Still largely in the clinical trial phase.
<i>Supportive Care</i>	Management of symptoms and treatment side effects, including infections.	Includes use of growth factors, antibiotics, and treatment of anemia and thrombocytopenia.

Prognosis

- **Variable Course:** The clinical course of CLL in children is not well defined due to its rarity. In adults, the prognosis varies widely based on genetic and molecular features.

Research and Future Directions

- **Need for More Data:** Given its rarity, more research is needed to understand the pathophysiology, clinical behavior, and optimal management of pediatric CLL.
- **Clinical Trials:** Participation in clinical trials can be crucial for accessing novel therapies and contributing to the understanding of this disease in children.